

FORM-PTO-1390
(Rev. 12-29-99)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

033248-017

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)

09/913752

INTERNATIONAL APPLICATION NO.
PCT/SIOO/00002INTERNATIONAL FILING DATE
17 February 2000PRIORITY DATE CLAIMED
19 February 1999

TITLE OF INVENTION

DIRECTLY COMPRESSIBLE MATRIX FOR CONTROLLED RELEASE OF SINGLE DAILY DOSES OF
CLARITHROMYCIN

APPLICANT(S) FOR DO/EO/US

Darja FERČEJ TEMELJOTOV, Milojka MOHAR, Mateja SALOBIR, Ljubomira Barbara REBIČ, Marko OPRESNIK


Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: RETURN POSTCARD

"Express Mail" mailing label No. E1832885319US.
Date of Deposit 8/12/01I hereby certify that this paper or fee is
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Service "Express Mail Post Office to Addressee:
service under 37 CFR 1.10 on the date indicated
above and is addressed to the assistant
Commissioner for Patent Washington, D.C. 20231.SENI MATANGI
(Typed or printed name of person mailing paper or
fee)Bradley
Signature of person mailing paper or fee)

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.50) 09/913752		INTERNATIONAL APPLICATION NO. PCT/SI00/00002		ATTORNEY'S DOCKET NUMBER 033248-017	
17. <input checked="" type="checkbox"/> The following fees are submitted:				CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1,000.00 (960) International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00 (970) International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00 (958) International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00 (956) International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 (962)					
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$ 860.00	
Surcharge of \$130.00 (154) for furnishing the oath or declaration later than 20 <input type="checkbox"/> 30 <input type="checkbox"/> months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	13 -20 =	0	X\$18.00 (966)	\$	0
Independent Claims	2 -3 =	0	X\$80.00 (964)	\$	0
Multiple dependent claim(s) (if applicable)			0 + \$270.00 (968)	\$	0
TOTAL OF ABOVE CALCULATIONS =				\$ 0	
Reduction for 1/2 for filing by small entity, if applicable (see below).				\$	-0
SUBTOTAL =				\$ 860.00	
Processing fee of \$130.00 (156) for furnishing the English translation later than 20 <input type="checkbox"/> 30 <input type="checkbox"/> months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
TOTAL NATIONAL FEE =				\$ 860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 (581) per property +				\$	0
TOTAL FEES ENCLOSED =				\$ 860.00	
				Amount to be: refunded	\$ 0
				charged	\$
a. <input type="checkbox"/> Small entity status is hereby claimed. b. <input checked="" type="checkbox"/> A check in the amount of \$ <u>860.00</u> to cover the above fees is enclosed. c. <input type="checkbox"/> Please charge my Deposit Account No. <u>02-4800</u> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. d. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>02-4800</u> . A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: T. GENE DILLAHUNTY BURNS, DOANE, SWECKER & MATHIS, L.L.P. P.O. Box 1404 Alexandria, Virginia 22313-1404 (650)622-2300			<div style="text-align: center;">  SIGNATURE </div> <div style="text-align: center;"> <u>T. Gene Dillahunt</u> NAME <u>25,423</u> REGISTRATION NUMBER </div>		

09/913752

JC03 Rec'd PCT/TO 17 AUG 2001

"Express Mail" mailing label No. EL 832885319 US
Date August 17, 2001

Date of Deposit Patent
Attorney's Docket No. 033248-017

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
)
Darja FERČEJ TEMELJOTOV et al.) Group Art Unit: Unassigned
)
Application No.: PCT/SI00/00002) Examiner: Unassigned
)
International Filing Date: 17 February 2000)
)
For: DIRECTLY COMPRESSIBLE MATRIX)
FOR CONTROLLED RELEASE OF)
SINGLE DAILY DOSES OF)
CLARITHROMYCIN)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231

Sir:

In the Claims:

In the above application, before examination thereof, please cancel claims 1-15 and enter the following substitute claims 16-28:

16. A pharmaceutical formulation for peroral single daily application, comprising clarithromycin or a derivative thereof and a mixture of a fatty and a hydrophilic component.
17. A pharmaceutical formulation according to claim 16, further comprising a surfactant.
18. A pharmaceutical formulation according to claim 16, further comprising a pH modulator.
19. A pharmaceutical formulation according to claim 16, wherein the fatty component comprises glyceryl behenate.

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20. A pharmaceutical formulation according to claim 16, wherein the hydrophilic component comprises hydroxypropyl methylcellulose of low viscosity.
21. A pharmaceutical formulation according to claim 19, wherein the hydroxypropyl methylcellulose has a viscosity of about 15 cP.
22. A pharmaceutical formulation according to claim 17, wherein the surfactant comprises sodium docusate.
23. A pharmaceutical formulation according to claim 18, wherein the pH modulator comprises a phosphate buffer.
24. A pharmaceutical formulation according to claim 16, characterized in that it is in the form of a tablet.
25. A pharmaceutical formulation according to claim 23, characterized in that the tablet is lacquered.
26. A pharmaceutical formulation according to claim 23, characterized in that on the tablet an acid-resistant coating is applied.
27. A process for the preparation of a pharmaceutical formulation for peroral single daily application comprising clarithromycin or a derivative thereof and a mixture of a fatty and a hydrophilic component, which comprises forming a homogeneous mixture thereof and direct compressing said mixture into tablet form without use of solvents.
28. A process according to claim 27 comprising sieving the homogeneous mixture prior to compressing the mixture into tablet form.

Examination and allowance of the above claims are respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: T. Gene Dillahunty
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Date: August 17, 2001

21/8/15

09/913752

DIRECTLY COMPRESSIBLE MATRIX FOR CONTROLLED RELEASE OF SINGLE DAILY DOSES OF CLARITHROMYCIN

Technical Field

(IPC: C 07 G 11/00, A 61 J 3/10)

The present invention belongs to the field of pharmaceutical technology and deals with the macrolide antibiotic clarithromycin and its derivatives.

In the narrow sense the present invention deals with a novel peroral pharmaceutical formulation for controlled release of clarithromycin or its derivatives, enabled by a novel combined matrix consisting of a fatty and a hydrophilic component, whereto a surfactant and a pH modulator can be added when an additional influence on the release profile of the active substance is desired.

Background of the Invention

Clarithromycin is a slightly alkaline, practically water-insoluble and acid-sensitive macrolide antibiotic. Its solubility decreases with increased temperature and increased pH. A daily dose amounting to 500 mg has to be embedded in a relatively small matrix since a tablet should not be too large to swallow, thus leaving only a relatively narrow space for optimization of biopharmaceutical and physical-technological properties of a formulation. Consequently, in the preparation of a 24-hour tablet we face the problem of a high dose of a poorly soluble active substance and at the same time the need to ensure a repeatable and pH-independent release of clarithromycin according to a specific selected optimal time schedule.

The commercially available peroral formulation of clarithromycin with extended release contains an alginate matrix, which is known for its high dependence of the release of the active substance on the pH, whose preparation technology includes, inter alia, time-consuming and expensive processes of wet granulation, drying and sieving

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and which frequently also exhibits non-repeatable dissolution profiles between different series and a slowing down of the dissolution due to aging.

Thus, the present invention is based on a need to find a simple, efficient and pH-independent formulation which will repeatably release clarithromycin over 24 hours, thereby minimizing the subjective influences with each single patient. The release rate has to ensure optimal concentrations of the active substance in blood in order to achieve therapeutic effects over a longer time period.

Prior Art

Clarithromycin is a semisynthetic antibiotic formed by methylation of erythromycin on a lactone position of C6. Its synthesis was described in US patents 4,331,803 and 4,672,109. It acts on Gram-positive bacteria and is used clinically due to the wide spectrum of antimicrobial activity. On the market it is present in the form of lacquered tablets, a suspension and extended-release tablets.

Various (per)oral formulations with clarithromycin are also described in the following patent literature:

JP patent 85/163,823 describes an oral drug containing clarithromycin and citric acid increasing the absorption of the antibiotic in the digestive tract, disintegrants, carriers and lubricants.

Withdrawn EP patent application No. 277,042 describes an oral pharmaceutical formulation with improved taste, with a coating made of special polymers (especially polyvinylacetal diethylaminoacetate - AEA) soluble in gastric juice and with average particle diameters under 60 μm .

US patent 4,808,411 describes a formulation with erythromycin or its derivatives and a carbomer, optionally in the form of particles of an ionic complex, coated with a polymer, whereat the particles can be suspended in a liquid carrier.

JP patent 89/42,625 describes the preparation of film-coated microgranules of a drug with sustained action, which, in addition to clarithromycin, also contain AEA and water.

Withdrawn EP patent application No. 302,370 and WO patent application No. 90/08,537 describe improved (per)oral formulations (oily solution, suspension, emulsion) of erythromycin and its derivatives for filling into soft gelatin capsules with N-methyl-pyrrolidone.

EP patent 420,992 describes a process for producing a taste-masked oral formulation comprising spraying a suspension of a drug into a cold aqueous solution of AEA.

US patent 5,017,383 describes a method of producing a finely coated pharmaceutical formulation comprising mixing frozen particles of a liquid medium with a drug and a coating in the form of a fine powder adhering to the surface of the particles.

US patents 5,599,556 and 5,609,909 describe the taste-masking of encapsulated clarithromycin particles with prolamine coatings prior to the preparation of a suspension.

WO patent application No. 96/34,628 describes a formulation with masked taste for oral administration (especially a dry syrup), containing an unpleasantly tasting drug, a high polymer soluble in the stomach (preferably AEA or Eudragit E) and a monoglyceride having a low melting point (preferably glyceryl monostearate) in a stable β -crystal form (transfer from meta stable α -form by means of shaking at an elevated temperature) and a method for masking the taste.

WO patent application No. 97/16,174 describes a process for water-granulation of a macrolide antibiotic with a carbomer (acrylic polymer).

US patent 5,705,190 describes a solid oral pharmaceutical formulation with controlled release containing a drug poorly soluble in water, a water-soluble alginate salt, a complex salt of alginic acid with a metal cation and an organic carboxylic acid facilitating the dissolution of the drug.

US patent 5,707,646 describes a formulation for oral administration (especially dry syrup) containing an unpleasantly tasting drug, a functional polymer (preferably AEA and/or Eudragit E) in a substance having a melting point at 40-120°C, a sugar alcohol (e.g. sorbitol) and a basic oxide (preferably MgO).

WO patent application No. 98/46,239 describes a pharmaceutical formulation with extended action containing an erythromycin derivative and a hydrophilic water-soluble polymer, showing, at oral administration, an improved taste profile and fewer gastrointestinal side effects in comparison to the usual formulation, and the preparation technology comprises, inter alia, processes of wet granulation, drying, sieving and milling.

Thus, in patent and other literature from this field there can be found numerous publications describing the composition and the preparation of various formulations with clarithromycin, but no literature source has been found that would describe such a simple process for the preparation of a clarithromycin formulation with controlled release, enabling a selected and pH-independent release profile of the active substance over 24 hours.

Description of Novel Solution with Examples

The object of the invention is a novel matrix for a controlled release of clarithromycin or its derivatives, which contains a mixture of a fatty, water-insoluble component

being the main carrier of sustained release, and of a hydrophilic component that in an aqueous medium swells, gels or thickens and thereby forms a viscous layer through which the solubilized, dissolved active substance diffuses, thus influencing the structure and consistency of the whole matrix.

To this basic matrix there may be added a wetting agent, a surfactant which softens the matrix and binds together both types of components and contributes to an easier solubilization of the active substance. The result is a matrix system which by means of a mixed mechanism of tablet erosion and diffusion releases the solubilized and/or dissolved active substance through the viscous layer.

In order to additionally influence the release profile of the active substance, to the matrix there may optionally be added a pH modulator, which is an alkaline substance, e.g. a phosphate buffer, influencing the portion of the released active substance in the stomach in relation to the intestine or decreasing the influence of the current level of acidity in any particular part of the digestive tract.

Among fatty components to be used in the embodiments of the present invention, the suitable ones are triglycerides of higher saturated fatty acids such as palmitic acid, stearic acid and behenic acid, preferably glyceryl behenate, hydrogenated oils (e.g. vegetable oils or castor oil), carnauba wax and similar. The content of the fatty component of the matrix amounts to about 10-36 % of the mass of a tablet.

Glyceryl behenate is a lipid substance, most frequently used as a lubricant, with an additional favourable property that in higher concentrations it sustains the release of active substances. Chemically, it is a mixture of glyceryl esters of behenic/docozanoic acid (C₂₂) with a low content of mono-behenate and a melting point of 69-74°C.

As the hydrophilic component there are selected substances which increase the viscosity of the micro-environment, are suspendable, stabilize the current viscous layer and may also have the ability to soften the fatty components of the matrix. Suitable

substances are alkyl-substituted cellulose ethers, preferably hydroxypropyl methyl-cellulose (HPMC), more preferably HPMC with low viscosity, fatty alcohols (e.g. cetyl, stearyl, cetostearyl alcohols), polysaccharides (e.g. xanthan gum, guar gum, acacia), adsorbents with a large specific surface (e.g. Mg-Al-silicates) and the like. The content of the hydrophilic component of the matrix amounts to about 5-18 % of the mass of a tablet.

HPMC is a cellulose ether, usually used for increasing the viscosity of the environment, but simultaneously it also influences the release rate of active substances. Used were low-viscous types of HPMC having viscosities (nominally for a 2 % aqueous solution at 20°C) up to about 40 cP and M_n up to about 20000 (determined by the method of osmotic pressures).

It has been found that by combining glyceryl behenate and HPMC there was obtained an exceptionally effective matrix for sustaining and controlling the release of the active substance, since in contact with an aqueous medium (also in the stomach) it swells and thereby loosens the lipid (glyceryl behenate) structure and makes possible a release of clarithromycin by diffusion through the viscous layer at a simultaneous erosion of the matrix i.e the tablet. The ratio between the lipophilic and the hydrophilic components may be between 2 : 1 and 10 : 1.

Among surfactants, anionic ones e.g. sodium docusate, sodium lauryl sulfate, and non-ionic ones can be used. The content of the surfactant amounts to about 0.5-3% of the mass of a tablet.

Sodium docusate is an anionic surfactant which in the given combination contributes to a more uniform wetting of the lipid structure and thereby facilitates the hydration and the swelling of the matrix and makes possible a repeatable diffusion of clarithromycin from the matrix.

Tablets with clarithromycin can also be lacquered, e.g. with a suspension based on a mixture of HPMC and hydroxypropyl cellulose (HPC), according to a conventional

process or the release profile of clarithromycin is modulated by the application of an acid-resistant coating such as HPMC-phthalate.

An excellent property of the formulation of the present invention in comparison to prior art is a simple preparation technology since all ingredients are, at room temperature, just homogeneously mixed together, sieved and directly compressed into tablets, therefore no water or any other solvents are necessary.

An important technological advantage of the formulation of the present invention is also the fact that there is no need for additional lubricants, since glyceryl behenate itself, as the carrier of release control, has good lubricating properties.

Dissolution rates of clarithromycin *in vitro* from two matrix samples with controlled release over 24 hours were measured at the temperature of 37°C, during the first hour at pH = 3.0 and during the subsequent 23 hours at pH 6.8. They are shown in Figs. 1 and 2.

The invention is explained but in no way limited by the following examples.

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Example 1

Composition of one tablet:	clarithromycin	500 mg
	glyceryl behenate (Compritol 888)	350 mg
	HPMC (E50-LV P)	150 mg
	lactose	150 mg

Dissolution test:

Dissolution profile is shown in Fig. 1.

Example 2

The composition was the same as in Example 1 only that instead of 34.5 g of lactose the same quantity of Na-docusate was used.

Example 3

Composition of one tablet:	clarithromycin	500	mg
	glyceryl behenate (Compritol 888)	350	mg
	HPMC (E50-LV P)	150	mg
	lactose	131.905	mg
	NaH ₂ PO ₄	49.538	mg
	Na ₂ HPO ₄	2.607	mg
	Na-docusate	5.95	mg

Dissolution test:

Dissolution profile is shown in Fig. 2.

Example 4

Composition of one tablet:	clarithromycin	500 mg
	glyceryl behenate (Compritol 888)	350 mg
	HPMC (E15-LV P)	150 mg
	polyvinyl pyrrolidone (K 25)	60 mg
	microcrystalline cellulose	40 mg
	stearic acid	15 mg
	SiO ₂ (Aerosil 200)	5 mg
	talc	5 mg
	Ca-stearate	25 mg

Example 5

Composition of one tablet:	clarithromycin	500 mg
	glyceryl behenate (Compritol 888)	350 mg
	HPMC (E50-LV P)	150 mg
	polyvinyl pyrrolidone (K 25)	60 mg
	microcrystalline cellulose	40 mg
	stearic acid	15 mg
	SiO ₂ (Aerosil 200)	5 mg
	talc	5 mg
	Ca-stearate	25 mg

Example 6

The composition of a tablet was the same as in Examples 1-5 only that on the tablet also an acid-resistant coating with the following composition was applied:

HPMC-phthalate	28.75 mg
triethyl citrate	2.875 mg
yellow pigment (Fe-oxide)	0.822 mg
TiO ₂	0.514 mg
talc	4.039 mg

Claims

1. A pharmaceutical formulation for peroral single daily application, characterized in that it contains clarithromycin or its derivatives and a mixture of a fatty and a hydrophilic component.
2. A pharmaceutical formulation according to claim 1, characterized in that in addition to the given components it contains a surfactant.
3. A pharmaceutical formulation according to claim 1, characterized in that in addition to the given components it contains a pH modulator.
4. A pharmaceutical formulation according to claim 1, characterized in that in addition to the given components it contains other pharmaceutically acceptable additives.
5. A pharmaceutical formulation according to claim 1, characterized in that the fatty component is glyceryl behenate.
6. A pharmaceutical formulation according to claim 1, characterized in that the hydrophilic component is hydroxypropyl methylcellulose of low viscosity.
7. A pharmaceutical formulation according to claim 6, characterized in that hydroxypropyl methylcellulose has a viscosity of about 15 cP.
8. A pharmaceutical formulation according to claim 2, characterized in that the surfactant is sodium docusate.
9. A pharmaceutical formulation according to claim 3, characterized in that the pH modulator is a phosphate buffer.

10. A pharmaceutical formulation according to claim 1, characterized in that it is in the form of a tablet.
11. A pharmaceutical formulation according to claim 10, characterized in that the tablet is lacquered.
12. A pharmaceutical formulation according to claim 10, characterized in that on the tablet an acid-resistant coating is applied.
13. A process for the preparation of a pharmaceutical formulation according to claim 1, characterized in that it comprises homogeneous mixing, sieving and direct compressing into tablets without use of solvents.
14. A pharmaceutical formulation for peroral single daily application, characterized in that it is prepared according to the process according to claim 13.
15. A pharmaceutical formulation according to claims 1 to 12 for use in the treatment and prophylaxis of bacterial infections.

Abstract

The invention refers to an improved pharmaceutical formulation for controlled release of clarithromycin or its derivatives, enabled by a novel combined matrix consisting of a fatty and a hydrophilic component, whereto also a surfactant and a pH-modulator may be added when an additional influence on the release profile of the active substance is desired.

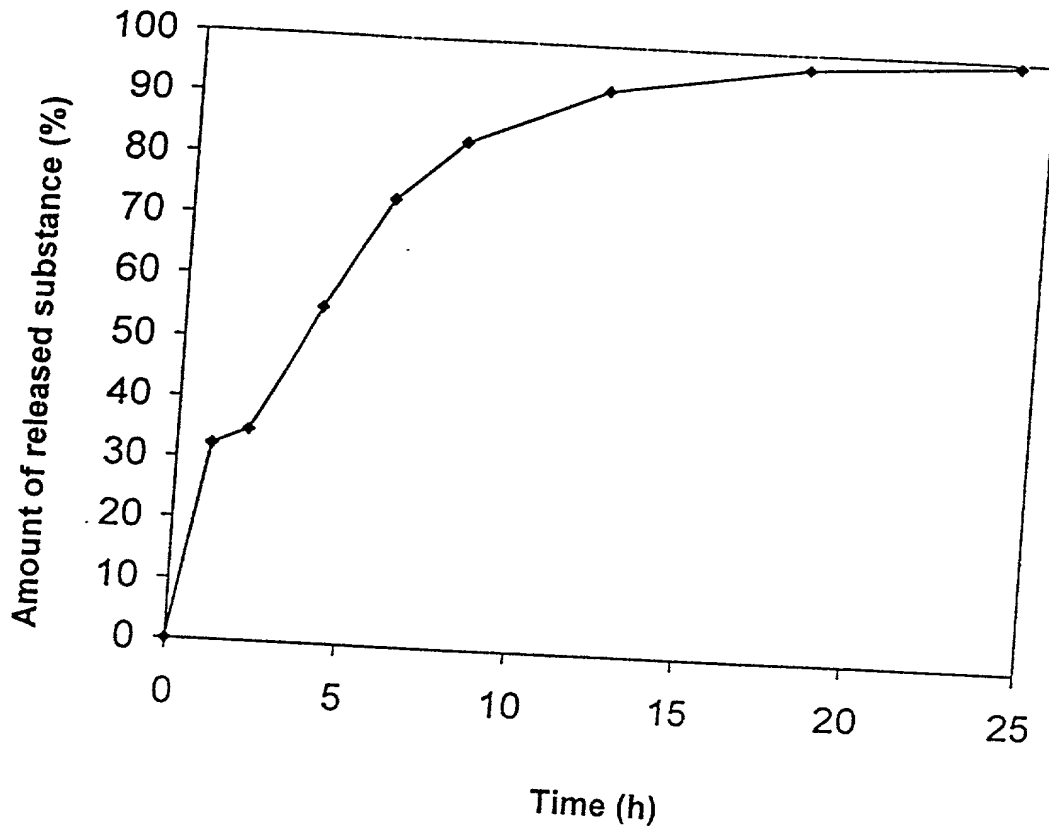


Fig. 1

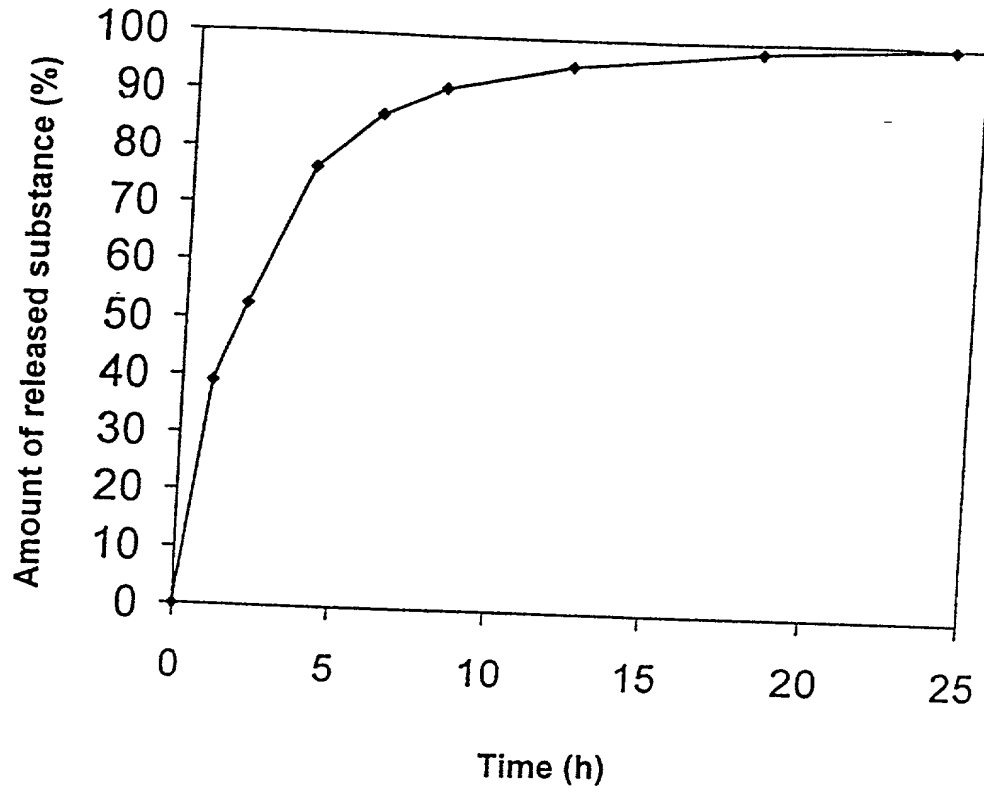


Fig. 2

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.

033248-017

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name:

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

DIRECTLY COMPRESSIBLE MATRIX FOR CONTROLLED RELEASE OF SINGLE DAILY DOSES OF
CLARITHROMYCIN

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Number _____

on _____

and was amended

on _____ (if applicable).

☒ was filed as PCT international application

Number PCT/SI00/00002

on February 17, 2000

and was amended

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
Slovenia	P-9900039	February 19, 1999	<u>X</u> Yes <u> </u> No
			<u> </u> Yes <u> </u> No
			<u> </u> Yes <u> </u> No
			<u> </u> Yes <u> </u> No
			<u> </u> Yes <u> </u> No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D)
(Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.

033248-017

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. §120:

U.S. APPLICATIONS		STATUS (check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)		
PCT/S100/00002	February 17, 2000		X	

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

William L. Mathis	17,337	Eric H. Weisblatt	30,505	Bruce T. Wieder	33,815
Robert S. Swecker	19,855	James W. Peterson	26,657	Todd R. Walters	34,040
Platon N. Mandros	22,124	Teresa Stanek Rea	30,427	Ronni S. Jellison	34,979
Benton S. Duffett, Jr.	22,030	Robert E. Krebs	25,885	Harold R. Brown III	36,541
Norman H. Stepko	22,716	William C. Rowland	30,888	Allen R. Batty	36,686
Ronald L. Grudziecki	24,970	T. Gene Dillahunty	25,423	Brian P. O'Shaughnessy	32,747
Frederick G. Michaud, Jr.	26,003	Patrick C. Keane	32,858	Kenneth R. Lentler	36,075
Alan E. Kopecki	25,813	B. Jefferson Boggs, Jr.	32,344	Fred W. Hathaway	32,236
Regis E. Shutter	26,999	William H. Benz	25,952	Wendi L. Weinstein	34,450
Samuel C. Miller, III	27,360	Peter K. Skitt	31,917	Mary Ann Dillahunty	34,576
Robert G. Mukai	28,531	Richard J. McGrath	29,195		
George A. Hovance, Jr.	28,223	Matthew L. Schneider	32,814		
James A. LaBarce	28,632	Michael G. Savage	32,596		
E. Joseph Gess	28,510	Gerald F. Swiss	30,113		
R. Danny Huntington	27,903	Charles F. Wichard III	33,096		


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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D)
(Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.

033248-017

FULL NAME OF SOLE OR FIRST INVENTOR <u>Daria PERČEL TEMELJOTOV</u>		SIGNATURE <u>D. F.</u>	DATE <u>27. 8. 2001</u>
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FULL NAME OF THIRD JOINT INVENTOR, IF ANY <u>Maja SALOBIR</u>		SIGNATURE <u>[Signature]</u>	DATE <u>27/8/01</u>
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FULL NAME OF FOURTH JOINT INVENTOR, IF ANY <u>Ljubomira Barbara REBIČ</u>		SIGNATURE <u>[Signature]</u>	DATE <u>27. 8. 01</u>
RESIDENCE <u>Dergomaška 50, 1000 Ljubljana, Slovenia</u>		CITIZENSHIP <u>Slovenia</u>	
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FULL NAME OF FIFTH JOINT INVENTOR, IF ANY <u>Marko OPRESNIK</u>		SIGNATURE <u>[Signature]</u>	DATE <u>08-27-2001</u>
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